SYNTHESIS OF LUPIN ALKALOIDS

BY

ROGER ELDON BEYLER

B.A., North Central College, 1944
A.M., University of Illinois, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
UNIVERSITY OF ILLINOIS, 1949

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ACKNOWLEDGMENT

The author wishes to express his appreciation to Professor Nelson J. Leonard for suggesting this investigation and for providing the counsel and inspiration which have made the research a stimulating experience.

He is also indebted to the University of Illinois for graduate assistantships and fellowships from 1946 to 1949, and to the Research Board of the Unversity of Illinois for a research grant during the summers of 1948 and 1949.

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SYNTHESIS OF LUPIN ALKALOIDS

Introduction

When this investigation was begun the lupin alkaloid sparteine had never been totally synthesized, although it had been known to chemists for nearly a hundred years and its structure had been established beyond any reasonable doubt (1,2). It was the purpose of this investigation to synthesize *dl*-sparteine, to resolve it into its optical antipodes, and to compare these with naturally occurring *d*- and *l*-sparteine.

It was predicted at the outset of this work that there should be six optical isomers, or three *dl* pairs, of the sparteine molecule. Any synthesis of the sparteine structure would be expected to give a mixture of these diastereoisomeric pairs. Since it is probable that any one or all of the six isomers are naturally occurring lupin alkaloids, a further aim of this research was to separate and characterize the racemates formed in the synthesis.

Discussion Of Results

Two methods for the synthesis of *dl*-sparteine were developed. The first method involved a single-step cyclization and reduction of 1-carbethoxy-4-keto-3-(α-pyridyl) pyridocoline by means of high pressure hydrogenation over copper chromite. The second method utilized an identical reaction of diethyl 2,4-di(α-pyridyl) glutarate. The 1-carbethoxy-4-keto-3-(α-pyridyl) pyridocoline was prepared from ethyl 2-pyridylacetate and ethyl orthoformate in the presence of acetic anhydride according to the method of Clemo, Morgan, and Raper (3). The preparation of diethyl 2,4-di(α-pyridyl)-glutarate was carried out by condensation of two molecules of ethyl 2-pyridylacetate with one molecule of formaldehyde or methylene iodide. Formaldehyde gave the better yield. Thus it is apparent that the synthesis of *dl*-sparteine by either route is a simple two-step process starting with ethyl 2-pyridyl-

acetate.

The *dl*-sparteine prepared by the above reductive cyclization methods was identified by preparation of the known mono- and dipicrate, and by conversion to the known *dl*-oxysparteine (4). Natural *l*-sparteine and synthetic *dl*-sparteine dissolved in chloroform showed identical infrared spectra.

The synthetic *dl*-sparteine was resolved by means of *l*- and *d*-β-camphorsulfonic acid and both *d*- and *l*-sparteine were obtained. *l*-Sparteine was identified by conversion to the known *d*-β-camphorsulfonate and dipicrate. *d*-Sparteine was identified by preparation of the known dipicrate and monoperchlorate. In each case mixed melting points of the salt of the resolved base with the salt of the naturally occurring base served to establish the identity. Further confirmation of the successful resolution was provided by the fact that the infrared spectra of resolved and naturally occurring *d*- and *l*-sparteine dipicrates were identical but differed slightly from the infrared spectrum of *dl*-sparteine dipicrate.

From the mixture of products obtained by either synthetic method a solid diastereoisomer of *dl*-sparteine was obtained. Fractional distillation, chromatography, and fractional crystallization of the perchlorates were used to effect separation of the diastereoisomeric pairs. The solid isomer was characterized as the monopicrate, dipicrate, and monoperchlorate. The only previously known solid isomer of the sparteine structure was the *levo*rotatory α-isosparteine prepared by dehydrogenation-hydrogenation of *l*-sparteine as carried out by Winterfeld and Rauch (5). This synthesis was repeated and infrared spectral comparison showed the solid isomer obtained by reductive cyclization to be the racemate of Winterfeld and Rauch's α-isosparteine. It is suggested that the latter compound be designated *l*-α-isosparteine and the synthetic racemate be referred to as *dl*-α-isosparteine in keeping with the general practices of previous investigators.

Thus two of the three possible racemic pairs have been obtained by the method of reductive cyclization. The third

theoretically possible racemate was not identified among the products of these two synthetic methods.

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VITA

The author was born on May 20, 1922, in Nappanee, Indiana. He received his elementary and high school education in the public schools of Naperville, Illinois, and was graduated in chemistry from North Central College in that city in 1944. From 1944 to 1946, he served in the United States Navy. In September, 1946, he entered the Graduate College of the University of Illinois and received the degree of Master of Arts in August, 1947. During the fall and spring semesters of 1946-1947 and 1947-1948 he was a part-time teaching assistant in organic chemistry. He held a University fellowship from September, 1948, to June, 1949, and a research grant from the Research Board of the University of Illinois during the summers of 1948 and 1949.

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